General

Guideline Title

World Gastroenterology Organisation global guidelines: celiac disease.

Bibliographic Source(s)

World Gastroenterology Organisation (WGO). World Gastroenterology Organisation global guidelines: celiac disease. Milwaukee (WI): World Gastroenterology Organisation (WGO); 2012 Apr. 25 p. [75 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: World Gastroenterology Organisation (WGO-OMGE). WGO-OMGE practice guideline: celiac disease. Paris (France): World Gastroenterology Organisation (WGO-OMGE); 2007. 18 p.

Recommendations

Major Recommendations

Diagnosis of Celiac Disease (CD)

Introduction

The considerable increase in the numbers of patients being diagnosed with CD correlates with the recognition of a remarkably wide variety of clinical manifestations of the disorder, the development of accurate screening tests, and also a true increase in the incidence.

In the clinical setting, a wide range of symptoms are observed:

- *Classical CD*: Mostly gastrointestinal symptoms (diarrhea, malnutrition, weight loss, steatorrhea and edema secondary to hypoalbuminemia).
- *Nonclassic*: In this category, patients may present with gastrointestinal symptoms (abdominal pain, gastroesophageal reflux symptoms, vomiting, constipation, irritable bowel syndrome-like symptoms, distension, bloating, borborygmus, etc.); or nongastrointestinal symptoms, also known as extraintestinal manifestations (without gastrointestinal symptoms). These patients are usually monosymptomatic or oligosymptomatic.
- *Asymptomatic CD (also formerly known as silent CD)*: The patient reports no symptoms at all, even in response to detailed questioning, despite the presence of a characteristic intestinal lesion. However, studies on the effect of a gluten-free diet (GFD) on patients who were asymptomatic at the time of diagnosis show improvement in their quality of life and thus support the decision to continue with dietary restriction in the long term.

This diversity of symptoms represents a challenge to health professionals who are not familiar with CD.

Current Diagnosis

In current practice, the diagnosis of CD (see Figure 2 in the original guideline document) hinges on a diagnostic intestinal biopsy and the concomitant presence of a positive CD-specific serology. A second (post-treatment) biopsy is not necessary for most patients if they respond satisfactorily to the specific treatment and should be reserved for patients in whom the first biopsy and serologic test are inconclusive (e.g., seronegative enteropathy) or for patients who are receiving a strict GFD but fail to respond. A gluten challenge, in which the offending agent is reintroduced while the patient is on a restrictive diet, should be reserved for patients who are receiving treatment but have a doubtful diagnosis.

Diagnostic Tests

Intestinal Biopsy

An intestinal biopsy together with positive serology represents the gold standard in diagnosing CD. 1992, Marsh reviewed the intensity of mucosal damage observed in treated CD patients who were confronted with increased amounts of gluten. A modified Marsh classification is now widely used in diagnosing CD in clinical practice.

Histological Characteristics of Celiac Enteropathy

Histological damage is considered characteristic, but not pathognomonic, of CD, as similar lesions are seen in several other disorders. CD affects the mucosa of the proximal small intestine, with damage gradually decreasing in severity towards the distal small intestine, although in severe cases the lesions can extend to more distal areas.

The severity and extent of the histological damage appear to correlate with the intensity of the clinical symptoms. The proximal damage may be very mild in atypical or silent cases, with little or no abnormality histologically detectable in the intestine. Abnormalities in the gastric and rectal mucosa may be observed in some cases.

The lesion in the duodenum/upper jejunum may be patchy, as a result of which it may be missed if there is insufficient mucosal sampling. At least four biopsy samples must be taken—three from the second part of the duodenum distal to the papilla, and one from duodenal bulb. A negative histological diagnosis may justify a second biopsy in selected patients who have positive autoantibodies such as endomysial antibodies (EMAs).

Biopsy samples taken from the proximal duodenum above the papilla of Vater may have artifacts (e.g., stretching of villi) produced by submucosal Brunner's glands, which may be falsely interpreted as flat mucosa.

Under light microscopy, the most characteristic histological findings in patients who are taking a gluten-containing diet are:

- Blunted or atrophic villi
- Crypt hyperplasia
- Mononuclear cell infiltration in the lamina propria
- Epithelial changes, including structural abnormalities in epithelial cells
- Intraepithelial lymphocyte infiltration

A series of well-designed studies by Marsh made it possible to interpret the wide range of mucosal damage induced by gluten, with the celiac histological modifications being categorized as ranging from normal mucosa to completely flat villi. The modified Marsh classification is widely used in clinical practice (see table below).

Table. The Modified Marsh Classification of Gluten-Induced Small-Intestinal Damage

Stage 0	Preinfiltrative mucosa; up to 30% of patients with dermatitis herpetiformis (DH) or gluten ataxia have small-intestinal biopsy specimens that appear normal
Stage 1	Increase in the number of intraepithelial lymphocytes (IELs) to more than 30 per 100 enterocytes
Stage 2	Crypt hyperplasia. In addition to the increased IELs, there is an increase in crypt depth without a reduction in villus height. Gluten challenge can induce these changes, which can also be seen in 20% of untreated patients with DH and celiac disease (CD)
Stage 3	Villous atrophy: A, partial; B, subtotal; C, total. This is the classic celiac lesion. It is found in 40% of DH patients. Despite marked mucosal changes, many individuals are asymptomatic and therefore classified as having subclinical or silent cases. This lesion is characteristic of, but not diagnostic of, CD and can also be seen with severe giardiasis, infantile food sensitivities, graft-versus-host disease, chronic ischemia of the small intestine, tropical sprue, immunoglobulin deficiencies, and other immune deficiencies and allograft rejection

Table. The Modified Marsh Classification of Gluten-Induced Small-Intestinal Damage

General Considerations on Histological Diagnosis

A small-bowel biopsy together with positive serology is the current gold standard for the diagnosis of CD. Histological findings are not pathognomonic of the disorder. However, histological examination does not always allow correct diagnosis of CD. A correct histological diagnosis requires a series of factors related to number of samples, sample quality, processing and reading.

In view of the subjective aspect of histopathological analysis, it is important to have access to pathology expertise (see table below).

Table. Key Factors to Be Considered for Ensuring Reliable Histological Diagnosis
• Number of biopsies procured • Quality of biopsy samples • Handling of samples • Patchiness of mucosal damage • Different grades of lesion • Subjective histologic interpretation

Role of Endoscopy in Patients with Suspected CD

During the last 20 years, upper gastrointestinal endoscopy has gained importance as a procedure allowing histological sampling of the mucosa, as it is less invasive and time-consuming than peroral biopsy. The endoscopic procedure also allows incidental observation of typical duodenoscopic features that are highly predictive of the disease. Although endoscopy may provide an indication for intestinal biopsy in patients who are being examined for other reasons than suspected CD, it may not be sufficiently sensitive to detect the disorder. The characteristic findings on endoscopy include:

- Scalloped folds, fissures and a mosaic pattern
- Flattened folds
- Smaller size and/or disappearance of folds with maximum insufflation

If endoscopy produces findings of this type, a duodenal biopsy becomes necessary. In contrast, a clinical suspicion of CD requires a small-bowel biopsy even when there is a normal duodenoscopic appearance.

Serum Antibodies for Suspicion and Diagnosis of CD

CD-specific serological tests, which have been in use for more than 20 years now, are important for 2 purposes: to select patients in whom biopsies are appropriate and to confirm the diagnosis in cases in which an enteropathy has been detected. A number of serological markers have been shown repeatedly in many studies to be highly sensitive and specific for untreated CD. On the basis of the target antigens, serologic tests for CD can be divided into 2 groups:

- *Autoantibodies*:
  - Antiendomysial (EMA) and anti-tissue transglutaminase (tTG) antibody tests
- *Antibodies targeting the offending agent (gliadin)*:
  - Conventional antigliadin antibodies (AGAs) (nowadays considered obsolete for diagnostic purposes)
  - Antibodies against synthetic deamidated gliadin peptides (DGPs)

All of these antibodies are based on immunoglobulin A (IgA) or immunoglobulin G (IgG). Specifically, IgG-based tests are useful for detecting CD in selected IgA-deficient patients.

IgA EMA

IgA EMA antibodies bind to endomysium, the connective tissue located around smooth muscle, producing a characteristic staining pattern that can be visualized with indirect immunofluorescence. The test result is reported simply as positive or negative, since even low titers of serum IgA endomysial antibodies are specific for CD. The test is expensive, observer-dependent, and labor-intensive, requiring expert input for correct interpretation. The target antigen has been identified as tissue transglutaminase (transglutaminase 2). IgA EMA testing is moderately sensitive (around 80%) and highly specific (with close to 100% specificity) for untreated (active) CD.

IgA tTG

The antigen against which EMAs are directed is tTG. Anti-tTG antibodies are highly sensitive and specific for the diagnosis of CD. Enzyme-linked immunosorbent assay (ELISA) tests for IgA anti-tTG antibodies are now widely available and are easier to perform, less observer-dependent, and less costly than the immunofluorescence assay used to detect IgA EMA antibodies. The diagnostic accuracy of IgA anti-tTG assays has been further improved by the use of human tTG instead of the nonhuman tTG preparations (with poorer diagnostic accuracy) used in earlier immunoassay kits. Today, tTG antibodies are used throughout the world, but there are still substantial differences between the different commercial kits available, the cut-off points suggested by the manufacturers, and standardization of laboratory techniques.

A rapid method of detecting antibodies to self-tTG antigen (red blood cells) released by hemolysis and forming complexes with tTG-specific IgA class antibodies has recently been developed. The test can be conducted within a few minutes, during a single consultation. The method can help with rapid decisions and its diagnostic accuracy appears to be very similar to that of the conventional tTG test. However, as the rapid test can have false-positive and false-negative results, it should not replace serological and histological diagnosis.

IgA AGA and IgG AGA Assays

Gliadins are the major components of the wheat storage proteins collectively termed gluten. Purified gliadin is readily available and is used as the antigen in ELISA tests to detect serum AGA. Serum AGA levels are frequently raised in untreated CD, and antigliadin assays have been used for some years as a diagnostic aid. Although these tests demonstrate moderate sensitivity and specificity, with the IgA tests being superior to IgG, their positive predictive value in the general population is relatively poor. AGA tests are no longer routinely recommended for diagnosing CD, because of their lower sensitivity and specificity. However, AGA tests are currently the only biomarkers that may be present in patients with non-celiac gluten sensitivity.

IgA and IgG DGP Antibodies

An ELISA-based on the detection of a combination of synthetically developed DGPs was introduced a few years ago, and clinical research has shown that this assay has a very high level of diagnostic accuracy in high-risk and low-risk populations—very similar to autoantibody testing. Studies have shown that detection of the IgG class is highly sensitive and specific for a suspicion of CD in general, and also for detection of the disorder in tTG-seronegative cases and in patients with selective IgA deficiency. More recently, the 2 DGP tests have been combined in a single assay, including IgA and IgG tTG determinations. Early studies show a high level of sensitivity but, as expected, low specificity. However, this may be improved in association with other tests.

General Considerations Regarding Serum Antibodies

The accuracy and reliability of serological tests were established in studies conducted in research settings in experimental conditions and may not reflect the level of accuracy in clinical practice. Studies reporting the best performance of antibody tests were carried out with selected cases and controls and/or in populations with a high prevalence of the disease. Testing for patients in low-risk populations has shown that the sensitivity and specificity of all antibody tests are affected. In low-risk populations, while the negative predictive values of different tests are very high, the positive predictive values are low. In this context, the diagnostic accuracy of serology might be improved by increasing the cut-off values to reach 100% positive predictive values, or by adding other serologic tests simultaneously or sequentially. With the last strategy, agreement of the results (with results of both tests positive or negative) would imply very high sensitivity, specificity, and positive and negative predictive values. Tissue transglutaminase antibodies appear to be of limited value in children under 2–3 years of age, and some studies have shown that DGP tests perform better and may allow better detection. It used to be the case that serological findings were usually negative in patients with mild enteropathy (Marsh grades 1, 2, or 3b). However, this was based on conventional AGAs and EMAs as the only biomarkers. With the introduction of tTG and DGP, the sensitivity for detecting patients with mild enteropathy (Marsh ≥2) has increased (see Table 3 in the original guideline document).

Choosing the Most Appropriate Serologic Test in Different Clinical Scenarios

1. *To confirm gluten dependence in patients with enteropathy (diagnosis)*: Both IgA EMA, IgA tTG and IgG, and IgA DGP perform similarly, offering the most valuable surrogates for gluten dependence. IgG DGP appears to be very helpful in IgA-deficient patients and for some EMA-negative and tTG-negative patients.
2. *To select patients for duodenal biopsy*: To reduce the need for duodenal biopsies, and on the basis of the different accuracy of serologic tests, a series of serological algorithms are used to select patients for biopsy in different clinical scenarios:
    - *From the general population (screening)*. tTG and DGPs show similar performance and have a high sensitivity. These tests have low positive predictive values in low-risk populations. A serologic algorithm, with serial use of more specific screening assays (e.g., EMA) has therefore been widely used to improve the diagnostic accuracy in the general population. Simultaneous or serial use of 2 tests (e.g., IgA and IgG DGP/tTG plus either IgA tTG or IgA DGP or IgG DGP) provides the highest positive and negative predictive values. A combination of tests therefore improves case finding.
    - *Case finding in high-risk populations*. Any of the given tests can be used as a single assay, as they all show similar performance—

as a single test, or in combination. A combination of tests does not improve case finding.

The EMA test requires expert observers, and ELISA tests for detecting tTG antibodies should therefore be recommended in settings with low expertise.

Clinical Aspects and Key Symptoms

1. In adults with classic CD:
    - Chronic diarrhea (formerly considered the most common symptom)
    - Weight loss
    - Anemia
    - Abdominal distension
    - Lassitude and malaise
    - Edema
2. In children with classic CD:
    - Failure to thrive, weight loss, short stature
    - Vomiting
    - Diarrhea
    - Recurrent abdominal pain
    - Muscle wasting
    - Irritable bowel
    - Hypoproteinemia
    - Irritability and unhappiness
3. In adults and children with non-classic CD. The presentation may be monosymptomatic or oligosymptomatic, or with low intensity:
    - Abdominal distension
    - Abdominal pain
    - Chronic fatigue
    - Iron-deficiency anemia
    - Chronic migraine
    - Dermatitis herpetiformis
    - Peripheral neuropathy
    - Folic acid deficiency
    - Reduced bone density
    - Unexplained infertility
    - Late menarche
    - Unexplained abortion

Asymptomatic Clinical Course

CD should be considered in the following cases (estimated prevalences are given in brackets, if available):

- First-degree and second-degree relatives of celiac patients (10% and 5%, respectively)
- Unexplained iron-deficiency anemia (3%–15%)
- Unexplained folic acid, iron, or vitamin B_{12} deficiency
- Reduced serum albumin
- Unexplained hypertransaminasemia (2%–9%)
- Osteoporosis and osteomalacia of premature onset (2%–4%)
- Recurrent abdominal pain or bloating
- Skin rashes
- Other autoimmune disorders: type 1 diabetes mellitus (2%–15%), thyroid dysfunction (2%–7%), Addison's disease, autoimmune hepatitis (3%–6%)
- Ataxia and idiopathic neuropathy
- Down's and Turner's syndromes (6% each)
- Irritable bowel syndrome (3%)

Why Is CD Difficult to Diagnose?

- Alternative diagnoses (often irritable bowel syndrome)
- The condition may be oligosymptomatic or asymptomatic
- The condition may have latent periods
- The complexity of the clinical presentation (systemic disease)
- Clinicians are unaware of the condition and there are several "myths", such as:
  - CD is rare
  - CD only occurs in Caucasians
  - CD occurs mostly in Europe and the United States
  - CD only occurs in childhood
  - CD only occurs in patients with chronic diarrhea
  - CD can be cured after (a period of) treatment

Differential Diagnosis

CD presents a very complex and protean clinical picture, and there are many diseases in which mucosal changes similar to those of CD are seen (see Table 4 in the original guideline document).

Why Should We Detect CD?

For symptomatic CD patients, the introduction of a GFD can lead to significant improvement in symptoms, abnormal biochemical measures, and impaired quality of life. Long-term treatment also reduces the risk of malignant and nonmalignant complications. Concerns remain about the long-term consequences in patients with asymptomatic CD and whether maintaining a lifelong GFD is necessary for all patients.

Patients with (long-term untreated) CD have an elevated risk for benign and malignant complications:

- Cancer (overall risk increment 1.35)
- Malignant lymphomas
- Small-bowel neoplasia
- Oropharyngeal tumors
- Unexplained infertility (12%)
- Osteoporosis (30%–40%)
- Bone fractures (increased risk for classically symptomatic CD patients) (35% increased risk)

Cascade for Diagnosing CD

Gold Standard: **Intestinal Biopsy and Celiac Disease (CD)-Specific Antibodies** ↓ **Medium Resources**
1. Antibody assessment as a single tool, as the only diagnostic measure when trained pathologists are not available • Anti-tissue transglutaminase (tTG) or endomysial antibody (EMA), or both (depending on availability and experience). Immunoglobulin A (IgA) assays are the most commonly used test with anti-tTG more sensitive but less specific than IgA EMA. • Immunoglobulin G (IgG) and/or IgA deamidated gliadin peptide (DGP) antibodies: These have a similar performance to IgA anti-tTG, and both DGPs are very useful for children under 3 years (in whom anti-tTG has poorer performance) and in IgA-deficient patients (use the IgG DGP test). 2. Intestinal biopsy: in settings in which pathology is available, perhaps remotely, but clinical laboratories cannot reach standards • Pitfalls in histological diagnosis are common and should be considered when biopsies are assessed by nonexpert pathologists. Findings are characteristic, but not specific. The strategy can be combined with the demonstration of clinical and/or histological improvement after introduction of a gluten-free diet (GFD)
↓ **Low Resources**
• A simple anti-tTG IgA test may be considered in low-resource settings. • Anti-tTG IgA can be assessed in the physician's office by using the self antibody-based rapid test, carried out on a fingertip blood sample. The test is simple, takes only a few minutes and has shown high sensitivity and specificity. • Endoscopic identification of duodenal markers indicative of mucosal atrophy is not diagnostic of CD, but strongly increases the suspicion of the disorder.

Note: A diagnosis only based on "clinical assessment" and improvement after a GFD should be strongly discouraged. This has been a source of misdiagnosis and can only be helpful in a minority of patients from the overall population (those with overt CD) and in areas with extremely limited resources. It could cause confusion making a nonspecific diagnosis of CD in patients with non-CD gluten sensitivity. The GFD can produce a nonspecific effect due to non–gluten-dependent dietary modifications or because of a "placebo effect" that may be falsely attributable to a CD diagnosis.

Management of CD

Introduction

The only treatment for CD is a strictly GFD for life. No foods or medications containing gluten from wheat, rye, and barley or their derivatives can be taken, as even small quantities of gluten may be harmful.

Oats are not toxic in over 95% of patients with CD, but there is a small subgroup (<5%) in whom oats are not safe. In addition, there is reluctance in some countries to advise liberal use of oats, because of difficulties in guaranteeing that commercially available oats are free of contamination with other grains. Rice and corn (maize) can be part of a GFD.

Complete removal of gluten from the diet of CD patients will result in symptomatic, serologic, and histological remission in most patients. Growth and development in children returns to normal with adherence to the GFD, and many disease complications in adults are avoided.

Approximately 70% of patients report an improvement in symptoms within 2 weeks after starting the GFD. With strict dietary control, antibody levels may decrease very soon after the diet has been instituted. In contrast, complete histological resolution is not always achieved, or may take years.

Although most patients have a rapid clinical response to a GFD, the rate of response varies. Patients who are extremely ill may require hospital admission, repletion of fluids and electrolytes, intravenous nutrition and, occasionally, steroids.

Patients with severe cases who require hospitalization are described as having a *celiac crisis*. Patients should be encouraged to eat natural high-iron and high-folate foods, especially if a deficiency in these minerals is documented. Patients should consult a dietitian who is knowledgeable about GFDs. Not all dietitians are familiar with the complexity of a GFD, and local or national support groups may provide most of the information required.

Recommendations After Diagnosis

The following is a summary of recommendations for follow-up after diagnosis and tools for monitoring adherence to a GFD, during the first year after diagnosis (with follow-up appointments every 3–6 months):

- Clinical visits: Check symptoms and laboratory tests. CD serology tests (best predictors: quantitative determination of DGP IgA and tTG IgA)
- Visit to an expert nutritionist: Assessment of nutritional status and adherence to a GFD based on an interview, a food diary, and the frequency of consumption (coinciding with the clinical visit)

Refer to Table 6 in the original guideline document for a list of grains, starches, and flours not permitted in a GFD.

Refer to Table 7 in the original guideline document for a list of gluten-free grains, flours, and starches allowed in a GFD.

Other Foods for a Basic GFD

- Milk, cream, buttermilk, plain yogurt
- All fresh meats
- Eggs
- Legumes: lentils, chickpeas (garbanzo beans), peas, beans, nuts, seeds
- Fruits: fresh, frozen, and canned fruits and plain juices without added ingredients
- Vegetables: fresh, frozen, and canned vegetables and plain juices without added ingredients
- Liquid vegetable oils

Miscellaneous

- Sweets: honey, corn syrup, sugar (brown and white)
- Snack foods: plain popcorn, nuts, and soy nuts
- Condiments: plain pickles, olives, nature herbs, pure black pepper, vinegars (apple or cider, distilled white, grape or wine, spirit)

Note: The majority of industrially produced foods contain non-allowable ingredients—attention to labeling is important, and available lists should be checked for allowable foodstuffs. It is very important to access a support group.

A GFD is low in fiber. Patients should be advised to eat a high-fiber diet supplemented with whole-grain rice, maize, potatoes, and ample vegetables. Any dietary deficiencies such as iron, folic acid, calcium and (very rarely) vitamin B_{12} should be corrected.

Monitoring

Lifelong strict adherence to the GFD is the best way of reducing risk and protecting against nonmalignant and malignant complications, whilst improving the patient's quality of life. Compliance is difficult. It helps if patients and relatives are well informed, if expert advice is available, and if progress and outcomes are monitored. Patients should be advised of the importance of strict adherence to the diet. Despite the importance of these aspects, there are no clear guidelines for assessing the outcome or for exploring adherence to the GFD.

The wide clinical variety of CD also makes it difficult to assess clinical activity using single measurements. It is possible that a multidisciplinary approach might produce more meaningful outcome information.

There is no consensus regarding the frequency of monitoring or the best measurements for assessing compliance and outcome. Helping patients adhere to the program is especially important in the first year. During this period, consultation with a professional team should take place every 3–6 months. After the first year and once the patient is stable, visits for consultation can be reduced to one per year.

Serological screening of first-degree and second-degree relatives should be considered.

Laboratory Assessment

Specific serologic tests should be less frequent, depending on the degree of compliance and the length of time spent on a GFD. Recent studies suggest that periodical testing for IgA DGP and/or IgA tTG is the preferred method for monitoring compliance. Although these tests do not identify minor dietary indiscretions, a continued reduction in serum concentrations helps to assess compliance with the diet.

Nutritionist Consultation

An expert dietitian should be consulted in order to:

- Assess the patient's current nutritional status
- Identify macronutrient and/or micronutrient intake and detect deficiencies and/or excesses. *It is important that patients with CD should consume adequate daily amounts of calories, thiamin, riboflavin, niacin, foliate, iron, calcium, and fiber.*
- Analyze eating habits and potential factors affecting access to the diet
- Provide information and initiate the GFD
- Provide dietary education
- Monitor and evaluate dietary compliance and reinforce alimentary counseling

Patients who are unable to adhere to the diet may require support with psychological counseling.

Persistence of Symptoms

Persistence of symptoms is almost always caused by continued ingestion of gluten. A common difficulty with the GFD is *cross-contamination* and the presence of unsuspected gluten in processed foods and/or medicines (although the latter is rare). Gluten may be a hidden ingredient, so it is prudent for patients to routinely check the ingredient list before purchasing any product; *available lists should be checked for allowable foodstuffs*. Serology can detect major and continued lapses in dietary adherence. Reasons for the persistence of symptoms include:

- Inadvertent gluten ingestion (this is the most common reason)
- Wrong diagnosis
- Lactose or fructose intolerance
- Other food intolerances
- Pancreatic insufficiency
- Microscopic colitis
- Bacterial overgrowth
- Collagenous colitis or collagenous sprue
- Irritable bowel syndrome
- Ulcerative jejunitis
- Enteropathy-associated T-cell lymphoma
- Refractory CD

The last 3 can be regarded as complications of long-lasting CD.

Refractory CD

A diagnosis of refractory CD is made when symptoms persist and when there is villous atrophy and failure to respond to a GFD. This may occur at presentation (primary), or after an initial response to a GFD (secondary). Refractory CD must be considered particularly in CD patients who are diagnosed over the age of 50.

There are 2 subtypes of refractory CD:

- *Type I*, with normal intraepithelial lymphocytes
- *Type II,* with clonal expansion of intraepithelial lymphocytes and an aberrant phenotype lacking CD3, CD8, and T-cell receptors

Type II disease is considered to be a form of low-grade intraepithelial lymphoma, revealed by severe malabsorption that is not responsive to a GFD. This is the most severe form and it is associated with a high mortality rate.

Clinical Algorithm(s)

A clinical algorithm titled "Diagnosis of Celiac Disease" is provided in the original guideline document.

Scope

Disease/Condition(s)

Celiac disease (CD)

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Screening

Clinical Specialty

Allergy and Immunology

Family Practice

Gastroenterology

Internal Medicine

Nutrition

Pathology

Pediatrics

Intended Users

Advanced Practice Nurses

Dietitians

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide guidelines for the diagnosis and management of celiac disease (CD)

Target Population

Patients with suspected or confirmed celiac disease (CD)

Interventions and Practices Considered

Diagnosis/Evaluation/Screening

1. Consideration of symptoms
2. Intestinal biopsy
3. Endoscopy
4. Histological tissue assessment
5. Marsh classification of gluten-induced small-intestinal damage
6. Serologic tests
    - Immunoglobulin A (IgA) endomysial antibody (EMA)
    - IgA anti-tissue transglutaminase antibody (tTG)
    - IgA and immunoglobulin G (IgG) deamidated gliadin peptide (DGP) antibodies
    - Conventional antigliadin antibodies (AGAs) (considered obsolete for diagnostic purposes)
7. Differential diagnosis
8. Serological screening of first-degree and second-degree relatives

Management

1. Gluten-free diet (GFD)
2. Clinical visits to check symptoms and perform laboratory tests (serology tests)
3. Visit to an expert nutritionist to assess nutritional status and adherence to a GFD
4. Correcting dietary deficiencies such as iron, folic acid, calcium and vitamin B_{12}, as needed
5. Hospitalization in severe cases
6. Lifelong monitoring of compliance to GFD
7. Managing persistent symptoms and refractory celiac disease

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Prevalence of celiac disease (CD) and CD symptoms
- Benign and malignant complications of CD
- Symptom resolution
- Mortality

- Quality of life
- Compliance

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

World Gastroenterology Organisation's (WGO's) 'Graded Evidence' System

WGO's 'Graded Evidence' system is built to help National Societies of Gastroenterology and all those interested in the practice and research of gastroenterology keep track of the literature in topics covered by WGO Guidelines. Most guidelines are based on evidence which is out of date as they appear. Sometimes the 'lag time' is as much as 2–3 years. WGO's Graded Evidence system bridges this gap. WGO Guidelines are constantly reviewed and updates are built when new information becomes available.

Level 1 Evidence is collected from PubMed and includes meta-analyses, systematic reviews, randomized controlled trials and evidence-based practice guidelines.

Gastroenterology and hepatology journals scanned:

- Gastroenterology
- Hepatology
- GUT
- Journal of Hepatology
- Nature Reviews Gastroenterology and Hepatology
- American Journal of Gastroenterology
- Seminars in Liver Disease
- Clinical Gastroenterology and Hepatology
- Endoscopy
- Gastrointestinal Endoscopy

General medical journals scanned:

- New England Journal of Medicine
- Lancet
- JAMA-Journal of the American Medical Association
- Annals of Internal Medicine
- PLOS Medicine
- BMJ - British Medical Journal
- JAMA Internal Medicine
- Canadian Medical Association Journal
- BMC Medicine
- Cochrane Database of Systematic Reviews

Graded Evidence is an iterative process - and for that reason need not be so concerned with searching both Medline, EMBASE and Biosis for example. All top gastrointestinal (GI) journals are covered by both Medline and EMBASE and in single one-off complex searches unique citations in one or the other are often due either to differences in database currency or differences in coverage of less important journals. In addition to cost issues, the generous republishing and copyright policies of the US National Library of Medicine (NLM) make Medline the preferred choice. The WGO Graded Evidence library is grateful to the NLM for making data available to clinicians and practitioners outside the US for free.

Search Strategies

Search strategies for each topic are based on a combination of controlled access and free text terms. The strategies aim for 'precision rather than 'sensitivity'. Highly sensitive search strategies as for example used by the Cochrane Collaboration when collecting literature reviews produce many irrelevant records. The advantage is these strategies retrieve all records which are relevant to a topic. But the 'number needed to read' is large and thus time consuming. Busy gastroenterologists probably prefer very precise search strategies in top GI journals and thus make sure every major article is found. The WGO Graded Evidence works along the lines of PubMed-Medline 'Clinical queries' features. Precise searches only find relevant information. Indexing errors may still be responsible for irrelevant or duplicate records. Case studies and animal studies are not usually included.

Graded Evidence records link directly to PubMed-Medline and from here the searcher can follow the various link options to find similar records or an indication of how to find full text.

Guideline-specific Methods

A literature search was conducted in Medline and EMBASE (on the EMBASE.COM platform) plus the Cochrane Library's Systematic Review database and CENTRAL database from the last ten years up to March 31, 2012.

In addition, the guideline committee is kept up to date with all current and new evidence through the World Gastroenterology Organisation's Graded Evidence and Evidence alert update services, as described above. Monthly searches are performed in Medline and EMBASE to identify high-level evidence for all guideline topic review panels. Scottish Intercollegiate Guidelines Network (SIGN) or McMaster hedges are used most often.

Number of Source Documents

- Meta-analyses, systematic reviews, practice guidelines: 38
- Clinical trials (randomised controlled trials only after 2012): 28

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Each citation is assessed in terms of the quality of an article and how relevant it is for the guideline topic in question. Articles are then scored by assigning one or several stars:

Grade Key

- Key Development – 3 stars
- Very Important – 2 stars
- Important – 1 star
- Special Mention – no star

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Graded Evidence

The World Gastroenterology Organisation (WGO) Guidelines Library contains practice guidelines written from a viewpoint of global applicability. WGO Guidelines are available in English, Spanish, Portuguese, French, Mandarin and Russian. WGO Guidelines go through a rigorous process of authoring, editing and peer review and are as evidence based as possible. Ultimate responsibility and editorial control lies with the WGO Guidelines Committee.

Each guideline includes references to other relevant guidelines. These are collected, summarized and re-published or linked-to by WGO for the benefit of members. In many instances, there will be more than one guideline. For example guidelines on Colorectal Cancer Screening are published by WGO, but the Scottish Intercollegiate Guidelines Network (SIGN) also publishes guidelines on this topic as does the New Zealand Guidelines Group and the Canadian Medical Association.

WGO is the only organisation, however, who has adopted a global focus. Cascade-based WGO guidelines offer different treatment options for diagnosis and treatment depending on the resources available. A cascade is a hierarchical set of diagnostic or therapeutic techniques for the same disease, ranked according to the resources available.

WGO Guidelines are globally applicable by the nature of their cascades, which identify other ways of achieving the best possible outcome by taking the available resources into account. In addition, each guideline review team includes non-Western experts with direct knowledge of conditions in their regions.

Guideline-specific Methods

An expert committee was convened to review the currency of the guideline. All communication was by email. All committee members received all Level 1 evidence from the relevant searches. The committee chair decided in case of controversy, and the committee agreed consensus.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

World Gastroenterology Organisation (WGO) Guidelines go through a rigorous process of authoring, editing and peer review and are as evidence based as possible.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- The introduction of a gluten-free diet (GFD) can lead to significant improvement in symptoms, biochemical measures, and quality of life.
- Long-term treatment reduces the risk of malignant and nonmalignant complications.
- Growth and development in children returns to normal with adherence to a GFD, and many disease complications in adults are avoided.

Potential Harms

The rapid anti-tissue transglutaminase (tTG) test can have false-positive and false-negative results and should not replace serological and histological diagnosis.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Foreign Language Translations

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

World Gastroenterology Organisation (WGO). World Gastroenterology Organisation global guidelines: celiac disease. Milwaukee (WI): World Gastroenterology Organisation (WGO); 2012 Apr. 25 p. [75 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2005 Feb (revised 2012 Apr)

Guideline Developer(s)

World Gastroenterology Organisation - Medical Specialty Society

Source(s) of Funding

World Gastroenterology Organisation (WGO-OMGE)

Guideline Committee

Review Team

Composition of Group That Authored the Guideline

Review Team Members: Julio C. Bai (*Chair*, Argentina); Michael Fried (Switzerland); Gino Roberto Corazza (Italy); Detlef Schuppan (Germany); Michael Farthing (United Kingdom); Carlo Catassi (Italy); Luigi Greco (Italy); Henry Cohen (Uruguay); Carolina Ciacci (Italy); Alessio Fasano (USA); Andrea González (Argentina); Justus H. Krabshuis (France); Anton LeMair (Netherlands)

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: World Gastroenterology Organisation (WGO-OMGE). WGO-OMGE practice guideline: celiac disease. Paris (France): World Gastroenterology Organisation (WGO-OMGE); 2007. 18 p.

Guideline Availability

Electronic copies: Available from the World Gastroenterology Organisation (WGO) Web site .

Print copies: Available from the WGO, 555 East Wells Street, Suite 1100, Milwaukee, WI 53202 USA; Phone: +1 (414) 918-9798; Fax: +1 (414) 276-3349; E-mail: info@worldgastroenterology.org.

Availability of Companion Documents

The following is available:

- Graded evidence. Professor André Elewaut and Professor John Fevery's essential reading. Electronic copies: Available from the World Gastroenterology Organisation (WGO) Web site .

Spanish, Portuguese, and Mandarin translations of the original guideline document are available from the WGO Web site .

Print copies: Available from the WGO, 555 East Wells Street, Suite 1100, Milwaukee, WI 53202 USA; Phone: +1 (414) 918-9798; Fax: +1 (414) 276-3349; E-mail: info@worldgastroenterology.org.

Patient Resources

None available

NGC Status

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